AMERICAN ASSOCIATION of PHYSICISTS IN MEDICINE

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Secretary
U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001
ATTN: Rulemakings and Adjudications Staff

Submitted by electronic mail to Celimar.Valentin-Rodriguez@nrc.gov

Re: Rubidium-82 Generators, Emerging Medical Technologies, and Other Uses of Byproduct Material [Docket ID NRC-2018-0297]

The American Association of Physicists in Medicine (AAPM)[1] is pleased to submit comments on the regulatory basis to support rulemaking for part 35 of title 10 of the *Code of Federal Regulations* (10 CFR 35). AAPM appreciates this opportunity to share our perspective to the U.S. Nuclear Regulatory Commission (NRC) with respect to establishing regulations for strontium-82/rubidium-82 generators (Rb-82 generators), emerging medical technologies (EMT), and other medical use considerations. Additionally, we are grateful for the NRC's willingness to extend the deadline for comments on this regulatory basis, especially when considering the broad scope of topics.

AAPM recognizes that regulation by guidance documents is not an ideal long-term practice. To that point, AAPM supports the NRC's regulatory basis and the pursuit of a more robust rule which can better address future applications of radioactive materials in medicine. In general, AAPM feels that the existing requirements from NRC guidance is sufficiently protective. If the current guidance is adopted without significant changes, then the resulting regulations will be adequate. Our comments provide both broad assessments as well as specific answers to the questions presented in the regulatory basis.

BROAD COMMENTS

AAPM believes that the current regulatory requirements are adequate to protect patients, occupational workers, and members of the public. NRC's regulatory basis establishes a sound

[1] The American Association of Physicists in Medicine (AAPM) is the premier organization in medical physics, a broadly-based scientific and professional discipline encompassing physics principles and applications in biology and medicine whose mission is to advance the science, education and professional practice of medical physics. Medical physicists contribute to the effectiveness of radiological imaging procedures by assuring radiation safety and helping to develop improved imaging techniques (e.g., mammography CT, MR, ultrasound). They contribute to development of therapeutic techniques (e.g., prostate implants, stereotactic radiosurgery), collaborate with radiation oncologists to design treatment plans, and monitor equipment and procedures to insure that cancer patients receive the prescribed dose of radiation to the correct location. Medical physicists are responsible for ensuring that imaging and treatment facilities meet the rules and regulations of the U.S. Nuclear Regulatory Commission (NRC) and various state regulatory agencies. AAPM represents over 9,000 medical physicists.

plan to formalize longstanding guidance documents into new rules within 10 CFR 35. Evaluation of new EMTs, and any subsequently formed regulatory requirements, must remain commensurate to the risks of those technologies. Diagnostic agents possess a different risk profile than therapeutics, the latter being capable of acute deterministic effects.

Radionuclide Generator Systems

Regarding generators, breakthrough of unintended nuclides is a patient safety matter. Additionally, users should understand the activities and doses associated with the intended use of radiopharmaceuticals. Standards development for these generators, appropriate testing, and essential maintenance should be captured early on during the U.S. Food and Drug Administration (FDA) approval process. The NRC may benefit from strengthened collaboration and coordination with FDA, or at least when new EMTs come to market. These protocols should not be left for an individual licensee to create once they receive the devices.

Generators are used at a variety of facilities. For instance, a private practice cardiologist could come to rely upon Rb-82 generators. Having the generator on site and with a short half-life daughter gives added flexibility to meet patients' needs (i.e., the licensee won't need to order and wait for a dose from an external pharmacy, the shorter half-life makes it is easier to perform additional studies on a patient). Alternatively, generators are commonplace in hospitals and centralized nuclear pharmacies. Any rule changes will need to take these various settings and their users into account.

Training and Experience

Training and experience (T&E) criteria are paramount to ensuring the safe implementation of radioactive materials in medicine. There is a delicate balance in setting T&E standards. Too high may unnecessarily block individuals from the profession and result in access to care. Too low and there is the risk of authorizing inadequately trained personnel who may generate otherwise preventable radiation hazards. AAPM feels that the NRC's current regulatory requirements, whether in rule or EMT guidance, are sufficiently protective. For the questions around T&E for specific device training and awareness, AAPM cautions against this for individuals not directly engaging with the device. For instance, radiation safety officers would only need general awareness and emergency procedure training, not device specific operations.

Dosage vs. Dose

In the rapidly growing area of novel radiopharmaceuticals, dosage (administered activity) is largely preferred to be included on the written directive rather than dose. This is because activity is a more direct measurement that is more conducive to assess. Dose is difficult to plan for and to verify given unique patient variabilities. Post-treatment imaging, for certain radionuclides, is a best practice step for verifying the accuracy and efficacy of a treatment. Unfortunately, not all facilities may be capable of the necessary imaging or dosimetric calculations required to determine dose. As it stands, post-treatment imaging is not reimbursable; facilities may opt out of performing it on those grounds alone. Until these barriers are remedied, it is most fitting to base written directives on dosage and not dose.

SPECIFIC COMMENTS

Section A.1 – Generator Systems

- *Question A.1.1: Please provide comments on the need for radiation safety officers to have specific training for all generator systems licensed under 10 CFR part 35, subpart D, "Unsealed Byproduct Material—Written Directive Not Required." If general awareness on radionuclide generators, including their functions and risks, is sufficient, explain why.*

  Requiring the radiation safety officer (RSO) to have specific training for all generator systems would be unnecessary. Radiation safety elements are shared and independent of the make and model of the generators. Contamination, shielding, exposure monitoring, security, and more are satisfactorily covered in the existing training requirements for RSOs. In decades past, generators existed at nearly every diagnostic facility. That practice has inverted over time, leaving most clinical facilities without on-site generators. Sites could have difficulty recruiting and retaining RSO with specific expertise on all generators.

- *Question A.1.2: Please provide comments on whether and how the NRC should allow the completion of dosage measurement after the beginning of an incremental administration for radionuclides other than Rb-82. How would such an allowance be bounded? What considerations should go into the expansion of this flexibility?*

  Reproducibility of the elution is essential for dosage measurements concurrent to incremental administrations from a generator. If the system proves reliable, then the outcomes will have limited variability. However, this is challenged if the elution quality is not consistent.

  Regarding the considerations for allowing this flexibility, establishing any boundary will require arbitrary thresholds to be used (which could create unnecessary difficulties for future technologies). Factors to consider:

  1. Using only short half-life radionuclides.
  2. Selecting generators incapable of certain dose levels (such as triggering medical event criteria, or an ability to cause deterministic health effects).
  3. Radioactive emission type or energies.
  4. The risk or severity of breakthrough.

  Another approach may be to evaluate if the generators can achieve their desired medical outcomes while not creating undue risk to patients. If so, then flexibility should be granted.

- *Question A.1.3: The NRC has found that AUs authorized under § 35.290, "Training for imaging and localization studies," have sufficient understanding of radionuclide generators, and the NRC is considering revising § 35.27, Supervision," to require device-specific training requirements for supervised individuals. Please provide comments with a rationale on whether § 35.290 AUs should also be required to have device-specific training for all radionuclide generators for which they supervise the use.*

  The AU needs to have general awareness for generators, but they do not need the same working knowledge consistent with a technologist who is performing an elution. Requiring this as a baseline criterion for § 35.290 can raise problems for training programs and facilities that don't have the specific devices on premises. Limited access to generators, whether in-house or through a partnering pharmacy, will create a hardship if AUs are meant to interact with each type.

Section A.2 – Intravascular Brachytherapy Systems

- *Question A.2.1: The NRC is considering adding a new section under subpart F to address the specific training and experience (T&E) requirements to be an AU for IVB and other uses under*

§ 35.401 (liquid brachytherapy, diffusion brachytherapy, and eye applicators). Please provide comments on the sufficiency of the T&E for AUs as outlined in the current EMT licensing guidance documents for IVB, liquid brachytherapy, and eye applicators. Specifically, the NRC is seeking comments on the knowledge topics encompassing the safety-related characteristics of these EMTs required for AUs to fulfill their radiation safety-related duties and supervision roles; the methods on how knowledge topics should be acquired; and consideration for continuing education, vendor training for new medical uses, and training on NRC regulatory requirements.

Current training requirements appear adequate. AAPM would not recommend anything additional at this time. For many EMTs, the only way a licensee can acquire training is through vendor supplied training programs, and this practice should be supported in the future rules.

Section A.3 – Liquid Brachytherapy Sources and Devices

- *Question A.3.1: The NRC has found that the hazards of liquid brachytherapy are similar to those of microsources and microspheres. Please provide comments with a rationale on whether the current definition of manual brachytherapy in § 35.2, "Definitions," should be revised to include liquid brachytherapy and exclude microsources or if liquid brachytherapy should be included in the newly proposed subpart I for microsources.*

  AAPM suggests increasing coordination with the FDA. Some of these technologies may be evaluated as devices, while others could be seen as drugs. There is opportunity for more consistency between NRC and FDA classification systems, and it would reduce confusion and ease the implementation for future applications.

  Liquid brachytherapy should go in the new subpart for microsources. Many of the safety considerations will be more akin to radiopharmaceuticals rather than conventional brachy seeds. The challenge will be when to delineate from a radiopharmaceutical therapy and a liquid brachytherapy treatment. This may be determined by the route of administration, preparation methods, and biophysical delivery mechanics.

- *Question A.3.3: The NRC is considering amending § 35.2 to define the term "source leakage" as it relates to liquid brachytherapy. For example, a possible leakage rate could be any leakage from a liquid brachytherapy source that results in a dose exceeding 0.5 Sievert (50 rem) dose equivalent to any individual organ other than the treatment site. Please comment on whether this limit is appropriate and explain why or why not. What types of limits for liquid brachytherapy device leakage should the NRC consider (e.g., activity-based, dose-based, external to the patient)?*

  This limit would be consistent with the current regulatory framework for medical events. Thus, it would be appropriate.

Section A.6 – Gamma Stereotactic Radiosurgery and Photon Emitting Teletherapy Units

- *Question A.6.1: Please provide comments on the need for model-specific training for radiation safety officers for certain 10 CFR part 35, subpart H devices. If model-specific training is needed, how should the NRC determine which devices would require such training?*

  RSOs do not require model-specific training, as the radiation safety aspects of the units do not vary greatly. Authorized medical physicists (AMP) would have detailed knowledge of those matters. The RSO should have general radiation safety training and awareness to safely conduct themselves and to advise others in proximity to the radiation devices/hazards.

- *Question A.6.2: Current NRC requirements in 10 CFR part 35, subpart H, are focused on components critical to patient and facility safety for the use of these devices. The proposed changes to subpart H focus on elements and objectives rather than specific components. Examples of elements include source output, source collimation, source position, source attenuation, patient safety, and facility safety. Please provide comments on other elements that should be considered.*

  Other elements worth considering include the geometric accuracy of imaging systems (usually X-ray, sometimes optical) used for patient positioning and monitoring should be verified. Image quality is a lesser concern, but it should also be verified.

  Generally, licensees (AMPs and AUs, specifically) should have the flexibility to choose their own appropriate calibration methods for the elements that must be checked. This could be based upon manufacturer guidance or industry consensus standards. If this is determined during licensing, then inspectors can verify these procedures are being followed. There are too many potential variables to build into a robust rule, and AAPM fears the rule will quickly become dated if the NRC attempts it.

- *Question A.6.3: Please provide comments on what types of objective tests the NRC should require for full calibration measures for 10 CFR part 35, subpart H devices. What functional elements should be considered for safety? AND Question A.6.4: Please provide comments on what types of objective tests the NRC should require for periodic spot-checks for 10 CFR part 35, subpart H devices. Additionally, what functional elements should be considered critical to safety?*

  One example for safety is the ability to perform an "emergency off", and this should always be verified.

  AMPs should be able to designate their own program criteria, procedures, and frequency of testing. Assuming it follows manufacturer guidance or industry consensus standards for the calibration and testing of these devices.

Section A.7 – Microsource Manual Brachytherapy

- *Question A.7.1: The NRC is considering defining a "microsource" in § 35.2 as microparticles and microspheres. What types of radiation (such as alpha, beta, gamma) should fit into the definition of "microsource"? Please include comments and a rationale for whether (1) microspheres should be limited to specific types of radiation or certain energies; (2) microsources should be limited to sealed sources with a Sealed Source and Device (SS&D) registry; (3) unsealed microsources should be required to have a SS&D registry; and (4) any additional changes are needed in the current regulations for microsource brachytherapy that would increase flexibility for future microsource brachytherapy.*

  This expands on the discussion in response to A.3.1, with respect to delineating between radiopharmaceuticals, liquid brachytherapy, and microsources. Microsources should be distinguished by how it is delivered and then how it remains fixed within the patient anatomy, as well as its physical form (i.e., solid granular materials). Radiopharmaceuticals will purposefully redistribute from their point of injection or infusion, but a microsource procedure would intentionally hold that material in place to treat a disease site. Microsources could be either sealed (purposefully encapsulated) or unsealed (a raw form material, it may not necessarily remain contained). Requiring a SS&D would be excessive if applied to all cases,

and it should only be used when appropriate (i.e., if there is a kit, delivery system, or some associated equipment essential for the safe and accurate delivery of the microsources).

(1) No, a microsource should not be limited by type or energy of the radiation it emits. Instead, it should be determined by how the radiation is distributed into the anatomy. Meaning, can it be delivered into the body with a method that constrains the radionuclide to a defined implantation region or a specific area. The type of radiation is only relevant in whether it will be clinically effective, but that is not relevant to this definition.

(2) No, the NRC's decision for a particular radionuclide therapy requiring an SS&D, or not, should be independent of the definition as a microsource. Deciding what applications require an SS&D should be more a function of device (or associated preparation or delivery equipment) complexity, manufacturing methods (i.e., encapsulated manually or "sealed" due to physical and chemical form), or behavior as a sealed material, rather than what subpart of the 10 CFR 35 regulates it. Otherwise, some future product may be licensed as a microsource and forced to acquire an SS&D when it may not make sense. Here again, this question presents opportunity for collaboration between the FDA and NRC, to achieve concurrence of what does or does not require an SS&D.

(3) This is essentially the same as (2) above. If a microsource is simply a raw physical and chemical form material that does not break down and redistribute throughout the body, then it should not require an SS&D. If it requires manufacturing practices (welding, encapsulation, machining, tolerances, etc.), or if it has some supporting equipment essential to safe delivery, then it may make sense to have an SS&D. Definitions for microsources and what requires an SS&D should be kept independent of one another.

(4) Key items that would need addressing:

1. Some microsources may end up more aligned with radiopharmaceuticals as opposed to the current classifications as sealed source brachytherapy.
2. New category for physics-based QA and testing, analogous to what is defined in 10 CFR 35 Subpart F.
3. New training and clinical experience pathways to support microsources within § 35.51 (the current rule heavily focuses on external beam treatments but could be more aligned with nuclear medicine physics).

- *Question A.7.3: As the complexity of the medical use of byproduct material increases, use of teams in medical care is becoming more common. Please provide comments on the fundamental elements of a successful team-approach program.*

  Fundamental elements required for a successful team approach is utilization of expert knowledge for available sources. In the case of microsphere therapy, this may include individuals with expertise in:

  1. Cancer management: interventional radiology or radiation oncology.
  2. Catheter placement and imaging: interventional radiology.
  3. Radiation dosimetry: interventional radiology, radiation oncology, nuclear medicine, medical physics.
  4. Safe handling of unsealed byproduct material: RSO, nuclear medicine, medical physics.

- *Question A.7.4: For microsource manual brachytherapy, please provide comments and a rationale for whether the before-implant written directive should specify the dose or activity.*

For standardization and reproducibility, activity is preferable as it is readily measurable and does not vary depending on volume of tissue treated. Therefore, activity should be utilized for the pre-implant written directive together with the intended total volume of treatment.

- *Question A.7.5: For microsource manual brachytherapy, please provide comments and a rationale for whether the after-implant written directive should specify the activity administered or the dose delivered to the treatment site.*

  Activity administered is preferable, as dose can present challenges seen in other treatments, such as prostate brachytherapy. Activity is more readily measured, providing for standardization and reproducibility. Post-implant written directives should then include the activity and target volume treated.

- *Question A.7.6: As required by § 35.41 for determining whether a medical event has occurred (as defined in § 35.3045), please comment on whether and why the NRC should require calculating and documenting the activity administered or the activity or dose specifically delivered to the treatment site. By what deadline (e.g., number of hours or days) should this determination be made?*

  Same as A.7.5 above, activity is preferable for determining if a medical event has occurred. However, radiation dose (not activity) can cause harm. Thus, the authorized user (AU), and likely the AMP, would perform dose calculations when observing an activity variation greater than 20%. The AU would include any patient consequences, whether from over or under-dosing, expected to result from the event in the report submitted to the corresponding regulatory agency (per § 35.3045(d)(1)(v)).

  Fortunately, there are now more software packages available to allow post-treatment dose evaluation. The time for determination of dose delivered will need to be extended to allow for this additional component of workflow, when applicable. 72 hours for completion of calculations should be reasonable.

- *Question A.7.7: For microsource manual brachytherapy, please comment on whether the NRC should require post-treatment imaging to confirm that the treatment was delivered in accordance with the written directive. Why or why not? What other mechanisms are available to confirm that the treatment was delivered in accordance with the written directive?*

  Post-treatment imaging is a best practice; however, requiring it could put strain on resource constrained facilities. There can be changes between MAA and Y90 distribution due to both intentional or unintentional factors. Ultimately, it is the distribution of Y90 microspheres that lead to efficacy or adverse events. Post-treatment Y90 SPECT/CT and Y90 PET/CT have two aspects:

  1. Qualitative - to verify that the intended treatment territory received the Y90-microspheres.
  2. Quantitative - to verify that the planned absorbed dose was delivered to the intended treatment target.

  Note, not all microsources have a well-substantiated and definitive imaging methodology to provide anything beyond a qualitative analysis. Requiring post-treatment qualitative reviews can make sense, but performing quantitative dosimetry is yet inchoate for regulatory suitability.

- *Question A.7.8: Please identify any tasks that would require an authorized medical physicist for the use of microsphere manual brachytherapy and identify whether and how the NRC*

should revise the training and experience requirements for authorized medical physicists in § 35.51, "Training for an authorized medical physicist."

Activities that may fall within, but are not exclusive to, the purview of the medical physicist are activity assay, waste assay, dosimetry calculations, treatment planning and QA, equipment calibrations, room survey, waste management, establishing procedures, timeouts, procedure checklists, program implementation, and general oversight. Of course, AAPM would be thrilled if all facilities performing these procedures had a qualified medical physicist on their clinical care team, but that may not be feasible and could reduce the number of facilities offering care. Additionally, microsphere treatments may not be taught currently as core curriculum in medical physics programs. This is something that AAPM will need to investigate further and work on enhancing in the future.

AAPM strongly encourages the NRC to revise the training and experience requirements for authorized medical physicists in § 35.51, "Training for an authorized medical physicist." 10 CFR 35.51 does not recognize the unique physical properties of microsources and the required training in § 35.51 is exclusively for external beam radiation beam, particle beam therapy, and sealed source brachytherapy. The NRC may wish to consider the medical physics subspecialty of "Medical Nuclear Physics" by the American Board of Radiology or "Nuclear Medicine Physics and Instrumentation" by the American Board of Science in Nuclear Medicine. Recognizing the need for nuclear medicine trained physicists and defining their responsibilities with respect to EMTs will raise awareness and could encourage more physicists to pursue that subspecialty. Engagement with the AAPM for medical physics training criteria is recommended. Training requirements listed under 35 Subpart F (§ 35.490) may also need revisions and adjustments.

- *Question A.7.9: Please comment on what types of use should be permitted for microsource manual brachytherapy, including whether the use should be limited to that approved in the sealed source and device registry. Please comment on why unsealed microsources without a unique delivery system should or should not be allowed.*

  Use devices based on device indication for use. So long as FDA rules are complied with, the application of medical devices for care and treatment should be left up to the physicians authorized to use them. Deviations from FDA approved treatment deliveries are considered off-label use, and patients should be informed prior to the use of the non-approved method. Limiting the beneficial scope of a product by what is approved in the SS&D will cause rigidity and perhaps unnecessarily restrict medical care decisions.

  If a microsource can be delivered safely, consistently, and to an overall positive effect for patients, then it should be allowed. Delivery systems may or may not be unique. Forcing each to have a unique delivery could add excess complexity, specific training, and ultimately errors to occur. If a single system can be utilized for multiple future microsource technologies, then it would simplify the processes. FDA (or if applicable, SS&D) approvals should specify what delivery equipment is or is not suitable for a particular microsource.

- *Question A.7.11: The NRC is considering establishing minimum safety procedures for microsources and requiring instructions to assure adequate protection of public health and safety. These changes are based on current EMT licensing guidance for yttrium-90 (Y–90) microspheres and expected new uses of microsources. Please identify and comment on other items that should be included in a new requirement for safety procedures and instructions for microsource manual brachytherapy.*

No additional safety precautions should be necessary. For instance, Y90 within the body would not cause risk to others given the short penetration of Y90 beta (max is < 1cm), lack of photon emission, and low yields for bremsstrahlung emission. All solid organs are greater than 1 cm deep within the body; therefore, implantation does not represent a significant exposure risk outside of the intended patient (other than possible leeching, which is accounted for in post treatment patient guidelines).

The FDA approves microsources as devices, and thus new manufacturers or devices can come to market under 510(k) approvals. This is something to keep in mind, as safety procedures and instructions will have less regulatory review when brought in under this pathway.

- *Question A.7.14: The NRC is seeking input on the 80 hours of classroom and laboratory training for interventional radiologists pursuing AU status for Y–90 microsphere and other microsource uses. The NRC in the current EMT licensing guidance for Y–90 microspheres includes a pathway for interventional radiologists to become AUs for Y–90 microspheres use. This pathway requires the interventional radiologist to demonstrate that they have 80 hours of classroom and laboratory training in specific topics and specific work experience important to radiation safety, in addition to demonstrating they have sufficient clinical interventional radiology and diagnostic radiology experience. Please comment on why 80 hours is or is not an appropriate amount of time to ensure these topics are adequately covered. Who should supervise the work experience to ensure the future AUs have adequate radiation safety knowledge and why?*

  There needs to be careful consideration to formalizing the 80 hours for interventional radiologists (IR) as a rule. While reasonable for IR, it may set a precedent for other specialties to become AUs with limited training and experience. Most often for Y90, an IR performs the procedure, but it is planned and supervised by a radiation oncologist or nuclear medicine physician. These individuals complete 700 hours of training in classrooms, laboratories, and through hands-on work experience. 80 hours will not produce the same level of practical knowledge as other AUs. The AU should be able to fully understand, execute, and supervise any standard or emergency operating procedures.

Section A.8 - Other Part 35 Changes: Training and Experience

- *Question A.8.3: Please comment on why the current structure for authorized medical physicist involvement in 10 CFR part 35, subpart F, "Manual Brachytherapy," is or is not sufficient. If not sufficient, what specific tasks or skills should be performed by an authorized medical physicist for manual brachytherapy?*

  10 CFR 35 Subpart F describes the various steps and activities associated with clinical manual brachytherapy. The language and scope of CFR 35 Subpart F is exclusively associated with sealed source brachytherapy, where individual radioactive seeds are measured and tracked. The situation with Y90-microspheres and other microsource therapies is different in that individual microsources can neither be measured nor tracked individually. Practically, the microsphere dosages are handled as unsealed radioactive materials. 10 CFR 35.404, 35.406 would need additional modifications, while other sections such as 35.415 and 35.432 needs significant revisions to accommodate Y90-microspheres. Training requirements listed under 35 Subpart F (35.490) may also need revisions and adjustments to accommodate Y90-microspheres.

SUMMARY

AAPM appreciates this opportunity to comment on the regulatory basis for 10 CFR 35, Rb-82 generators, and EMTs. Over the last two decades, § 35.1000 served its purpose well in allowing new radiological technologies into clinical use, and we suspect that it will continue to do so. With sufficient operational and regulatory experience, devices such as Y90 microspheres are ready to move into their own formalized section of rules. AAPM looks forward to seeing future proposed rules that will result from this regulatory basis and comment period.

If we can provide any additional information, please contact AAPM's Senior Government Relations Manager, David Crowley (david@aapm.org).

Sincerely,

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